IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Philip A. Beachy et al.	Art Unit:	1625
Application No.:	10/573,945	Examiner:	Robinson, Binta M.
Filed:	March 7, 2007	Conf. No.	2047
Title:	HEDGEHOG PATHWAY ANTAGONISTS		

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Dr. Philip A. Beachy, do hereby declare that:

1. I am a co-inventor of the subject matter described and claimed in U.S. Patent Application No.: 10/573,945, entitled "Hedgehog Pathway Antagonists" that was filed on March 7, 2007, which is the U.S. national stage filing of International Patent Application No.: PCT/US04/32482, filed Sept. 29, 2004, which claims the benefit of priority to U.S. Provisional Application No.: 60/507,164, filed Sept. 29, 2003.

2. I have reviewed the Office Action dated January 5, 2010, in the subject application, including the rejection under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, and submit this Declaration to provide evidence to the Examiner in support of the patentability of the presently claimed invention, which is directed to compounds of Structure (I), (II), and claim 24.

3. The Examiner has alleged that the specification of the subject application is not enabling for the presently claimed compounds of Structures (I), (II), and claim 24 because no data has been disclosed with regard to the efficacy of the claimed compounds in inhibiting Hedgehog pathway signaling. Therefore, the Examiner concludes that the skilled artisan would encounter undue experimentation to

determine which of the claimed compounds have efficacy in inhibiting Hedgehog pathway signaling.

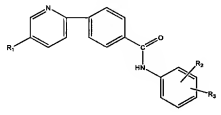
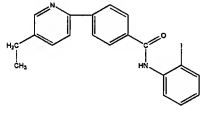
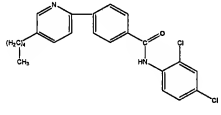
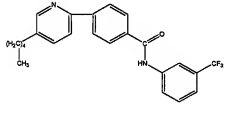
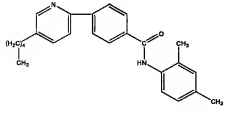
4. Scientists working under my direction carried out studies in accordance with the teachings of the subject application to screen the compounds disclosed in the specification for the ability of these compounds to modulate a Hegdehog signaling pathway.

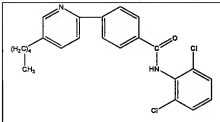
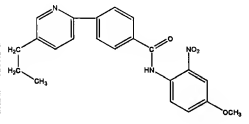
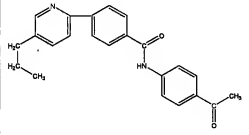
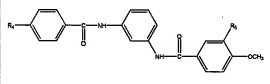
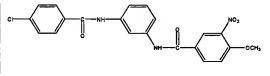
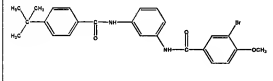
5. The procedure we carried out is as follows:

   A. Shh-LIGHT2 cells were created by stably transfecting NIH-3T3 cells, with a Gli responsive firefly luciferase reporter, a TK promoter- Renilla luciferase control, and a vector encoding G418 resistance (pSV-Neo), using Fugene 6 (Roche) transfection reagent. Transfected cells were selected with G418 and cell cloning.

   B. Shh-LIGHT2 cells were treated with ShhNp (4 nM) and candidate Hedgehog pathway modulating compounds for two days and then the luciferase activities were measured from the cell lysates by luminometry using a dual luciferase assay (Promega). Gli responsive firefly luciferase activity was normalized to control TK-Renilla luciferase activity. Compounds were tested in varying concentrations to determine the concentration of each compound required to achieve 50% inhibition of Sonic hedgehog induced Gli responsive firefly luciferase reporter activity (IC50).

6. Exemplary results that we obtained for compounds of Structures I (compounds1-7) and II (compounds 8-9) are shown in the following Table:

Compound Structure	Compound Number	IC50
	Structure 1	-
	1	750 nM
	2	100 nM
	3	100 nM
	4	60 nM
	5	60 nM

		
	6	250 nM
	7	500 nM
	Structure II	-
	8	100 nM
	9	1000 nM

7. The results show that compounds of Structure (I), (II), and claim 24, bearing each of the presently claimed classes of R groups have a common physiological activity of inhibiting a Hedgehog signaling pathway. Compounds 1-7 of Structure (I) have alkyl R_1 groups such as ethyl, propyl, and pentyl, and R_2 and R_3 groups such as hydrogen, alkyl, halogen, alkoxyl, acetyl and nitro groups. Compounds 8-9 of Structure (II) have R_5 groups such as chlorine and *tert*-butyl, and R_6 groups such as bromine and nitro groups.

8. Accordingly, in the context of the presently claimed compounds as a whole, the various presently claimed R groups contribute to a common physiological activity of inhibiting a Hedgehog signaling pathway. Thus, the exemplified compounds are representative of the genus of presently claimed compounds of Structure (I), (II), and claim 24.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the captioned patent application or any patent issued therefrom.

4/30/10
Date

Philip A. Beachy